Day–night blood pressure variations: mechanisms, reproducibility and clinical relevance

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One of the great advantages offered by ambulatory blood pressure monitoring (ABPM) is the possibility to describe BP patterns over 24 h under daily life conditions. This has produced a deeper insight into BP physiology, as well as into the association of certain diseases with characteristic circadian BP profiles. Subsequent to the application of the pioneering techniques for intra-arterial beat-by-beat ABPM over 24 h [1], it has become clear that BP is far from being maintained at a fixed level. Instead, BP shows continuous and often marked fluctuations [2] with a variety of time constants, ranging from a few seconds to hours, days and months, as in the case of seasonal BP fluctuations [3,4]. Analysis of 24-h ABPM data has allowed a quantitative description of BP variability. This is the case when considering all BP changes at the same time, summarized by the standard deviation of the 24-h average BP. This is also the case when focusing on specific components contributing to overall BP variance, such as the morning BP rise and the nocturnal BP fall [3,5].

The BP fall occurring at the time of night sleep is among the components of BP variability that have received the greatest attention by both physiologists and clinicians. The many studies investigating the mechanisms underlying these diurnal BP changes have highlighted the role played by several factors, such as central neural influences related to sleep stages, with a major contribution by the autonomic nervous system, humoral factors such as corticosteroid hormones and the renin–angiotensin system, and respiratory factors related to the mechanics of ventilation and the accompanying changes in arterial blood O_2 and CO_2 concentrations [3,6].

In 1988, O'Brien *et al.* [7] reported for the first time that an abnormal circadian blood pressure profile with decreased night-time dipping may lead to a higher risk of stroke. Subsequent studies of populations [8–11] and hypertensive cohorts [12–18] provided corroboration that an elevated nocturnal blood pressure is a harbinger of an unfavourable outcome. In spite of the apparent concordance between these large-scale outcome studies [8–18], several potential limitations require further clarification with respect to the prognostic accuracy of daytime versus night-time ambulatory blood pressure. Many studies considered only fatal outcomes [8,9,16,17] or did not have the power to study cause-specific cardiovascular endpoints [8,9,11,15]. Investigators dichotomized the night-to-day blood pressure ratio, and applied different definitions of dipping status or the daytime and night-time intervals. Few reports formally compared the predictive value of the blood pressure at night over and beyond the daytime level. Finally, in predominantly treated cohorts of hypertensive patients, antihypertensive drug treatment attenuated the association between outcome and blood pressure [13].

An additional important problem to consider in this field is the reproducibility of BP changes between day and night. Such a reproducibility and, as a direct consequence, the reproducibility of patients' classification into dippers and nondippers is indeed still a matter of lively debate. In this issue of the Journal, Hernandez-del Rey *et al.* [19] provide additional data on this topic originating from the National ABPM Registry of the Spanish Society of Hypertension. This was done by obtaining 48-h ABP recordings from 611 hypertensive patients, 235 of whom were yet untreated, recruited throughout Spain. The aim of the study was to investigate the reproducibility of the circadian ABP pattern over a 48-h period, by comparing day–night BP changes observed during the first 24-h period of ABPM with those observed during the second 24-h period, as well as with the mean day–night changes over the entire 48-h recording. The percentage of patients classified as nondipper for the first 24 h, the second 24 h and, on average, over the entire 48-h period was 47, 50 and 48%, respectively. When comparing the first with the second 24-h intervals, 24% of patients switched their classification from dipper to nondipper, or vice versa, with consistent results, when separately considering systolic and diastolic BP or treated and untreated patients. The conclusion drawn by the authors is that the categorization of essential hypertensive patients, investigated in a general practice setting, into dippers or nondippers based on a single 24-h ABPM is only moderately reproducible because one out of five patients changes her/his circadian BP profile classification

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over the next 24 h. Concerning the question of whether a longer duration of ABPM (e.g. 48 h) might provide more reliable data on day–night BP changes, the authors suggested that the average day–night BP difference derived from two 24-h periods may be more reproducible than that quantified by the analysis of one 24-h period only. A precise demonstration of this, however, is not provided in their study, in which no repetition of 48-h ABP recordings over time is available, whereas the comparison made by the authors between the day–night BP changes during the first 24 h and those averaged over 48 h is methodologically questionable [19].

The reproducibility of circadian BP profiles has been investigated in a number of previous studies (Table 1) [19–30], with differing results that were influenced by a number of factors. These include the methods selected to assess the day–night BP changes, the focus on treated or untreated subjects, the patients' concomitant clinical conditions, and the degree of daytime physical activity [31] or the quality of night-time sleep [24], although controversial data have been published also on this issue [32,33].

Chaves *et al.* [28] investigated the reproducibility of the dipping status in 101 subjects, including both normotensive and treated hypertensive patients, in whom 24-h ABPM was performed three times at intervals of 8–15 days. When the dipper/nondipper status was defined based on a predefined cut-off point (nocturnal BP reduction higher or lower than 10% of daytime BP levels, respectively), such a definition was poorly reproducible in the subsequent recordings. Conversely, when the percentage BP decline was analyzed as a continuous rather than as categorical variable, the average nocturnal BP fall was not different between recordings. Chaves *et al.* [28] did not report comparisons between recordings within individual subjects. Ben-Dov *et al.* [29] retrospectively examined the reproducibility of BP dipping at night in clinical practice patients with duplicated ABPM by accounting for the sleep–awake states, rather than by relying on arbitrary day–night definitions. They found that systolic BP dipping was equally reproducible as the average 24-h BP, with 66% of patients showing a reproducible dipping status. In their study, awake BP included also BP recorded during night-time arousals, whereas sleep BP also included BP recorded during afternoon naps. In a number of other studies, however, a limited reproducibility was reported for nocturnal BP fall in hypertensive patients. Palatini *et al.* [20] analyzed data from 508 patients included in the HARVEST trial, comparing BP dipping observed in two ambulatory recordings performed 3 months apart, and concluded that the reproducibility of night-time BP dipping was poor. Mochizuki *et al.* [22] assessed the day–night BP changes in 253 never-treated hypertensive patients and found a 29% variability in the dipper/nondipper definition between repeated recordings, whereas Manning *et al.* [24] reported a variability of approximately 50%. James *et al.* [21] reported that more than one-third of 42 elderly hypertensive patients modified their dipping status over a 2-month period. Omboni *et al.* [23] found that approximately 40% of hypertensive patients included in SAMPLE (Study on Ambulatory Monitoring of Pressure and Lisinopril Evaluation) changed their dipping pattern when ABPM was repeated after 1 year. Finally, the reproducibility of nocturnal BP dipping can be importantly affected by other diseases in the presence of hypertension. Rahmana *et al.* [27] investigated 59 hemodialysis patients, in whom the ambulatory BP was monitored for 44 h on three occasions, at baseline and after 6 and 12 months, respectively. The overall reproducibility of the dipper/nondipper classification was poor: 55% of patients maintained their original classification at 6 months and 70% at 12 months. However, when the nondipper status was considered separately, 92% of initially nondipper patients remained nondippers at 6 and at 12 months. The authors concluded that haemodialysis

Table 1 Reproducibility of nocturnal blood pressure fall

Study	Type of patients	Reproducibility
Palatini *et al.* (1994) [20]	Hypertensive	Poor
James *et al.* (1995) [21]	Hypertensive elderly	65%
Mochizuki *et al.* (1998) [22]	Hypertensive	71%
Omboni *et al.* (1998) [23]	Hypertensive untreated or treated	60%
Manning *et al.* (2000) [24]	Hypertensive	50%
Covic *et al.* (2000) [25]	Haemodialysis	As above
Peixoto *et al.* (2000) [26]	Haemodialysis	57%
Rahmana *et al.* (2005) [27]	Haemodialysis	55–70% (6–12 months) Nondipping 92%
Chaves *et al.* (2005) [28]	Normotensive and treated hypertensive	Poor (categorical analysis) High (considering blood pressure fall as a continuous variable)
Ben-Dov *et al.* (2005) [29]	Hypertensive accounting for sleep and awake periods	66%
Cuspidi *et al.* (2006) [30]	Hypertensive with or without diabetes	84.6% (dipper), 91.3% (nondipper) in diabetic hypertensive 49.2% (dipper), 29.5% (nondipper) in nondiabetic hypertensive
Hernandez-del Rey (2007) [19]	Hypertensive general practice	76% (24-h ABPM) 89% (48-h ABPM)

ABPM, ambulatory blood pressure monitoring.

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patients identified as nondippers consistently reproduce the same circadian profile over long-term follow-up, which is in agreement with the data provided by Covic *et al.* [25], but not in line with the results obtained by Peixoto *et al.* [26]. The latter study showed a reproducibility of nondipping of between 53 and 78% in the same type of patients. Similar results on a high short-term reproducibility of the nondipping pattern have been shown by Cuspidi *et al.* [30] in 36 hypertensive patients with type 2 diabetes, as compared with 61 untreated nondiabetic hypertensive subjects, by performing 24-h ABPM twice over a 4-week period. Some 91.3% of diabetic hypertensive patients, who were nondippers at the first recording, showed the same circadian pattern during the second ABPM, with the reproducibility of the dipping pattern being 84.6%. Conversely, in nondiabetic hypertensive patients, reproducible dipper and nondipper patterns were observed only in 49.2 and 29.5% of patients, respectively. The practical conclusion of the authors was that a nondipper pattern appears to be reliable in diabetic subjects, even if assessed by a single performance of 24-h ABPM, whereas repeated ABP recordings should be recommended to define the circadian BP pattern in a correct manner in nondiabetic individuals.

An international consortium [34] recently reported risk estimates independently associated with the daytime and night-time BP in 7458 subjects (mean age = 56.8 years; 45.8% women), enrolled in prospective population studies in Denmark, Belgium, Japan, Sweden, Uruguay and China. Median follow-up was 9.6 years. Adjusted for daytime BP, night-time BP predicted total ($n = 983$; $P < 0.0001$), cardiovascular ($n = 387$; $P < 0.01$) and noncardiovascular ($n = 560$; $P < 0.001$) mortality. Conversely, adjusted for night-time BP, daytime BP predicted only noncardiovascular mortality ($P < 0.05$), with lower blood pressure levels being associated with increased risk. Both daytime and night-time BP consistently predicted all cardiovascular events ($n = 943$; $P < 0.05$) and stroke ($n = 420$; $P < 0.01$). Adjusted for night-time BP, daytime BP lost prognostic significance only for cardiac events ($n = 525$; $P \geq 0.07$). Adjusted for the 24-h BP, the night-to-day BP ratio predicted mortality, but not fatal combined with nonfatal events. Antihypertensive drug treatment removed the significant association between cardiovascular events and the daytime BP. Thus, in the international database [34], the predictive accuracy of the daytime and night-time BP and the night-to-day BP ratio depended on the disease outcome under study and differed for fatal outcomes compared to the composite of fatal and nonfatal diseases [34]. For fatal endpoints, night-time BP performed better than the daytime BP, and the night-to-day BP ratio predicted mortality. By contrast, for fatal combined with nonfatal outcomes, the daytime BP performed equally as well as the night-time BP and the night-to-day BP ratio lost its prognostic accuracy. Antihypertensive drug treatment was a major confounder because patients with more severe hypertension and those with a history of cardiovascular complications were at the highest cardiovascular risk but, at the same time, were also more likely to be treated. Hypertensive patients take their medications during daytime and the blood pressure-lowering activity often weans off at night. This mechanism predictably leads to lower daytime BP, higher night-time BP, and a diminished night-to-day BP ratio.

Reverse causality might also contribute to the inconsistency in the prediction of disease outcomes by the night-time as opposed to the daytime BP. The international consortium reported that reverse dippers, who had higher night-time than daytime BP, were at the highest risk of all-cause mortality [34]. In several studies [14,17,35], reverse dippers not only were more frequently on antihypertensive drug treatment [14,17], but also they were older [14,17,35] or more likely to have a history of diabetes mellitus [35] or previous cardiovascular disease [14,35]. Moreover, similar to cardiovascular risk, the night-to-day BP ratio also increases with advancing age [36]. In the international database [34], participants with a systolic night-to-day BP ratio of 1 or more were older and therefore at higher risk of death, but they died at an older age than those whose night-to-day ratio was normal (≥ 0.80 to < 0.90). Thus, reverse dipping might be a marker rather than a cause of a worse outcome. The inverse associations in the international database [34] between noncardiovascular mortality and the daytime BP and between total mortality and the daytime BP in untreated subjects also supported the interpretation of reverse causality.

In conclusion, the classification of patients into dippers and nondippers depends heavily on arbitrary criteria, is poorly reproducible, and has a different prognostic meaning according to the disease outcome under study, the prevailing 24-h BP level, and treatment status. We would therefore recommend that, in future studies, any categorical results of the night-to-day BP ratio be supported by continuous analyses adjusted for the 24-h BP and be stratified for treatment status. Moreover, the available evidence supports the concept that the ambulatory BP should be recorded over the whole day, as both the night-time and daytime BP levels carry prognostic information. The 24-h BP level [37], rather than the dipping pattern, should continue to inform clinical decisions.

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Reproducibility of the circadian blood pressure pattern in 24-h versus 48-h recordings: the Spanish Ambulatory Blood Pressure Monitoring Registry

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Objectives **To assess the reproducibility of the circadian blood pressure (BP) pattern over a 48-h period by comparing the first 24 h of ambulatory blood pressure monitoring (ABPM) with the following 24 h and with the mean over 48 h.**

Patients and methods **Patients undergoing 48-h ABPM within the National ABPM Registry of the Spanish Society of Hypertension, based on 800 Spacelabs 90207 monitors distributed throughout Spain in hypertension units and primary healthcare centres, were included. Between June 2004 and September 2005, 611 valid 48-h ABPM recordings were obtained, 235 corresponded to patients without antihypertensive treatment.**

Results **The percentages of patients classified as non-dipper for the first 24 h, the second 24 h and the 48-h average were 47, 50 and 48%, respectively. When the first and second 24-h periods were compared, 147 (24%) subjects switched from dipper (D) to non-dipper (ND) or vice-versa. When the first 24-h period was compared to the 48-h average, 66 (11%) subjects switched patterns. The proportions were similar separately for systolic blood pressure (SBP) and diastolic blood pressure (DBP) and between treated and untreated patients. In subjects with poor ABPM reproducibility, night-to-day ratios were of an intermediate value between those of subjects always classified as D or ND.**

Conclusion **Categorization of D or ND based on a single 24-h ABPM is moderately reproducible, since one out of every five patients change profile over the following 24 h. Nevertheless, the use of 48-h ABPM in clinical practice should be assessed according to cost-effectiveness criteria. Night-to-day ratios may be helpful in identifying patients with a stable profile.** ***J Hypertens*** **25:2406–2412 © 2007 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Ambulatory blood pressure monitoring (ABPM) provides information on blood pressure (BP) during the activities of daily life and sleep, allowing the circadian BP profile to be defined [1,2]. Cross-sectional studies have shown that subjects with a non-dipper (ND) profile who do not display nocturnal BP reductions, have more severe target organ damage than dipper (D) subjects, whose nocturnal BP is at least 10% lower than daytime levels. It has been reported that ND have higher levels of urinary albumin excretion [3,4], a greater progression of renal failure [5,6], a higher prevalence of left ventricular hypertrophy [7] and a greater likelihood of heart failure [8]. The ND profile has also been associated with angiographic coronary artery stenosis in men [9], an increased prevalence of silent cerebrovascular disease [10,11] and a higher rate of ischaemic and haemorrhagic stroke [12]. Prospective studies have indicated that ND have more cardiovascular events than D [13–15], with respect to both hypertensive and normotensive subjects [14]. Therefore, the 24-h BP profile may be useful in assessing cardiovascular risk [16].

The classification of patients as D or ND on the basis of a single 24-h monitoring period should, however, be approached with caution, since one of the main drawbacks of the circadian BP profile is its limited reproducibility [7,17–19]. Although absolute values for 24-h, daytime and night-time BP are reasonably reproducible over a short period under the same conditions, the

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circadian BP profile changes between 20 and 45% in subjects in a second ABPM performed a few weeks or months later [7,17,19,20]. The reliability of the circadian BP profile classification is important due to its prognostic implications. In addition, it has been reported that the association between the ND profile and left ventricular hypertrophy or microalbuminuria is stronger in patients with a reproducible ND profile than in those with a variable profile [7,21].

Given the limited reproducibility of a single 24-h ABPM, the question is whether more prolonged BP recordings could improve the reliability of the circadian BP pattern classification. The main aim of this study was to analyse the reproducibility of the circadian BP profile in 48-h recordings, based on data from the National ABPM Registry of the Spanish Society for Hypertension. The first 24 h of recording were compared with the following 24 h and with the mean for the 48-h period. As a secondary objective, differences in the night/day ratio between subjects whose circadian BP profile changed from the first to the second 24-h period and those who did not were compared.

Methods

Patients

Patients from the National ABPM Registry of the Spanish Society of Hypertension were included. Between June 2004 and September 2005, a total of 20 000 valid ABPM recordings according to the project criteria were performed [22]. This study analysed 611 recordings from patients with 48-h ABPM. Inclusion and exclusion criteria for the registry were defined by the accepted indications for ABPM [23,24]: patients with suspected white-coat hypertension, patients with variable symptomatic hypertension over a 24-h period, hypertensive patients at high cardiovascular risk, and patients with treatment-resistant hypertension were included. Patients could present concomitant indications for ABPM. Subjects with an arm circumference of more than 42 cm, atrial fibrillation or other arrhythmias that could interfere with BP recording were excluded.

National Ambulatory Blood Pressure Monitoring Registry of the Spanish Society of Hypertension

The National ABPM Registry of the Spanish Society of Hypertension is a healthcare, teaching and research project based on the introduction throughout Spain of 800 ABPM devices (Spacelabs Medical, model 90207; SpaceLabs Inc., Redmond, Washington, USA) for use in daily clinical practice by primary care professionals and specialists in hypertension. The monitors are connected by Internet (www.cardiorisc.com) and linked to the case report form, in which a minimum number of mandatory variables are collected for each patient. Full details of the registry are described elsewhere [22,25]. Following validation, the data set is integrated in a single registry. All clinical investigators participated in a 3-h seminar/workshop, which provided training in the monitoring technique, the indications for ABPM, and the use of the technology platform.

The general information recorded in the case report form included: reason for ABPM, sociodemographic data, vascular risk factors and use of antihypertensive medication during the previous 2 weeks and during ABPM (type of drug, total daily dose and treatment regimen). Clinical measurements of BP and heart rate were the mean of two recordings obtained with a mercury sphygmomanometer or a validated semi-automatic device, according to the 2003 guidelines of the European Society of Hypertension/European Society of Cardiology [23].

Signed informed consent was obtained for all patients included in the registry, which contains no identifiable patient information, in compliance with Spanish law. The project was approved by the corresponding clinical research ethics committees and health authorities.

Ambulatory blood pressure monitoring

ABPM was preferentially performed on a normal day and the cuff used was appropriate to the size of the arm. The length of ABPM, type of cuff (normal or obese), and time of sleep and waking for each 24-h monitoring period were recorded. The interval between clinic BP measurement and ABPM was no more than 4 weeks.

Recordings were considered valid according to the project criteria when the percentage of valid readings was at least 80% of the total and there was no hour for which no readings were available. At least 14 measurements were required during the period of activity and/or a minimum of 7 during the rest period.

The 611 recordings analysed in this study corresponded to patients who met the general quality criteria and had daytime working hours and a night-time rest period of at least between 0100 and 0500 h. The D profile was defined as a reduction in systolic (SBP) and diastolic blood pressure (DBP) of at least 10% during the night compared with the period of activity [1]. All other subjects were classified as ND. Day and night periods were defined on the basis of the patient diary. The night/day ratio of SBP and DBP was calculated for four groups: subjects who maintained the same circadian BP profile in both 24-h periods (D-D and ND-ND) and those whose profile changed between the two periods (D-ND and ND-D).

Statistical analysis

After an initial descriptive analysis, patients with and without antihypertensive treatment were compared according to the demographic, clinical and biochemical variables recorded. Quantitative variables were tested for

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Table 1 Demographic characteristics and cardiovascular risk factors in treated and untreated patients

Variable	All ($n=611$)	Treated ($n=376$)	Untreated ($n=235$)	P value[#]
Age (years)	58 (13)	61 (12)	54 (13)	<0.001
Sex, male[a]	341 (56)	203 (54)	138 (59)	0.252
Waist circumference (men >102 cm, women >88 cm)	99 (16)	87 (23)	12 (5)	<0.001
BMI (kg/m^2)	29 (5)	30 (5)	28 (4)	<0.001
Diabetes	110 (18)	93 (25)	17 (7)	<0.001
Smoking	95 (16)	49 (13)	46 (20)	0.029
Dyslipidaemia[b]	235 (38)	160 (43)	75 (32)	0.007
Cardiovascular disease	60 (10)	54 (14)	6 (3)	<0.001

Values are mean (standard deviation). BMI, body mass index. [a] n (%). [b] Definition of dyslipidaemia was that of the European Society of Hypertension/European Society of Cardiology guidelines 2003 [23]. [#] Statistical comparisons between treated and untreated patients.

normality and were compared between groups using the Student's t-test or the Mann–Whitney test. Differences in qualitative variables between different groups of subjects were analysed with the chi-squared test or Fisher's exact test. McNemar's test was applied for the pairwise comparison of the proportion of non-dippers between the different monitoring periods.

Comparisons of 24-h day and night BP measurements between the first and second 24-h periods were made with the Student's t-test for paired data or the Wilcoxon test.

The differences between the means of the night/day ratios between the four groups of patients, defined on the basis of change or stability of the circadian profile between the two 24-h periods, were assessed by analysis of variance; the Bonferroni adjustment was applied to post-hoc group comparisons. A Bland and Altman graphical technique was applied, by plotting the difference of night/day ratios between the first 24-h and the second 24-h periods for each subject against their mean, both for SBP and DBP ratios. Those differences of night/day ratios between the two monitoring periods were used to estimate a coefficient of repeatability for the whole sample, and then separately for treated and untreated patients [26].

The cut-off for statistical significance was $P=0.05$. Data were analysed using the SPSS statistical package, version 13.0 (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 611 subjects were included, of which 235 (38.5%) were not receiving drug treatment (64 of these untreated patients were normotensive at the initial visit). The mean age was 58 ± 13 years, 341 (56%) were men, and the mean baseline BP was $149\pm19/87\pm11$ mmHg; the mean BP was $150\pm20/86\pm12$ mmHg for patients receiving antihypertensive treatment and $146\pm16/89\pm10$ mmHg for untreated patients. SBP was significantly higher in patients receiving treatment ($P=0.006$), while DBP was higher in untreated patients ($P=0.012$). The mean heart rate in treated and untreated patients was 74 ± 12 and 74 ± 11 bpm, respectively ($P=0.767$). Patients not receiving antihypertensive treatment were younger, less obese and had fewer cardiovascular risk factors than those receiving treatment, except for the rate of smoking (Table 1). Among treated patients ($n=376$), 35% were on monotherapy, 28% were receiving two drugs and 37% three or more antihypertensive drugs. Antihypertensive medication was administered in the morning in 78% of treated patients, at bedtime in 11%, both in the morning and night in 10%, and only two patients had their medication distributed in three doses per day.

Ambulatory BP values over 48 h and during the first and second day are shown in Table 2. The difference in BP between the two periods of activity was 1.55 mmHg [95% confidence interval (CI), 1.04–2.06; $P<0.0005$] for SBP and 0.98 mmHg (95% CI, 0.64–1.31; $P<0.0005$) for DBP. No significant differences in the values of SBP were observed between the two nocturnal periods, while a difference of 0.50 mmHg (95% CI, 0.09–0.90; $P=0.017$) was observed for DBP.

An ND pattern was observed in 47% of patients in the first 24 h, 50% in the second 24 h ($P=0.248$) and 48% for the mean of 48 h ($P=0.712$ when compared with the first 24-h period). The ND profile was more common in treated than untreated patients, both for the whole 48-h period (55 versus 36%, $P<0.0005$) and separately for the first 24-h and second 24-h periods (Fig. 1).

Table 2 Ambulatory blood pressure: average blood pressure over 48 h and differences between the first and second 24-h monitoring periods

	Mean	Standard deviation	P value*
SBP			
48-h day	133	14	
48-h night	120	15	
DBP			
48-h day	81	10	
48-h night	69	10	
SBP			
1st 24-h day	134.1	14	<0.0005
2nd 24-h day	132.5	14	
SBP			
1st 24-h night	120.3	16	0.081
2nd 24-h night	119.9	15	
DBP			
1st 24-h day	81.1	11	<0.0005
2nd 24-h day	80.1	11	
DBP			
1st 24-h night	69.0	10	0.017
2nd 24-h night	68.5	10	

DBP, diastolic blood pressure; SBP, systolic blood pressure. * Comparing the first 24 h of BP monitoring with the following 24 h.

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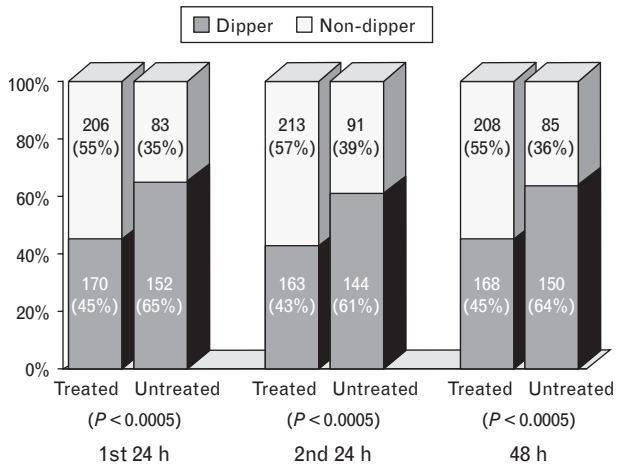
Fig. 1



Differences in the circadian blood pressure pattern between treated and untreated patients.

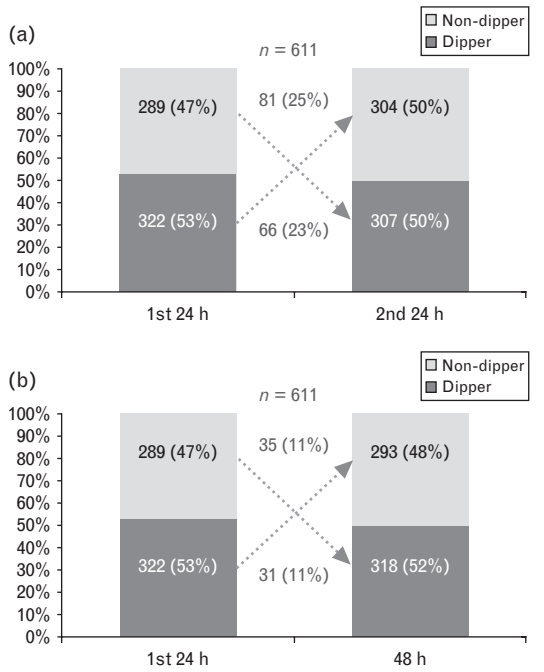
Office BP control (office BP less than 140/90 mmHg) was achieved in 156 (25.5%) subjects. The proportion of ND pattern in the whole 48-h period was 50.6% in patients with BP control and 47.0% in those without BP control ($P = 0.436$). Neither was there any statistically significant difference in the proportion of ND between patients with and without BP control when treated and untreated subjects were analysed separately (treated patients: 57.6 versus 54.6%, $P = 0.611$; untreated patients: 40.6 versus 34.5%; $P = 0.385$).

When the reproducibility of the circadian BP profile was analysed, comparison of the first and second 24-h periods revealed that 66 individuals classified as D in the first 24 h were classified as ND for the second 24 h, while 81 individuals changed from a classification of ND in the first period to D in the second period. In total, the circadian BP profile changed in 147 (24%) patients between the two periods (Fig. 2a). The same analysis was performed separately according to treatment status. Circadian BP profile changed from one period to the other in 52 out of 235 patients (22%) not receiving drug treatment, and in 95 out of 376 treated patients (25%) ($P = 0.377$) [Table 3(i)].

When the first 24-h period was compared with the mean for the 48-h period, 31 individuals classified as D for the first 24 h were classified as ND for the mean of 48 h, while 35 individuals classified as ND were classified as D for the mean of 48 h. In total, the circadian BP profile changed in 66 (11%) subjects (Fig. 2b). Neither was there any statistical difference in the proportion of changes according to the treatment status [$P = 0.869$, Table 3(ii)].

Table 4 shows the night/day ratios of SBP and DBP for the mean of 48 h and each of the two 24-h periods for the four groups of patients. Night/day BP ratios for subjects whose circadian profile changed differed significantly from those of subjects with a stable profile. The night/day ratio increased progressively in the following order:

Fig. 2



Changes in circadian blood pressure pattern. (a) Between the first and second 24 h. 147 (24%) subjects shifted from dipper (D) to non-dipper (ND) or vice-versa ($P = 0.248$). (b) Between the first 24 h and the mean of 48 h. 66 (11%) subjects shifted from D to ND or vice versa ($P = 0.712$).

Table 3 Changes in circadian blood pressure pattern in treated and untreated patients between the first and second 24 h and between the first 24 h and the mean of 48 h

Treatment status	First 24-h monitoring	Dipper	Non-dipper
(i) Between the first and second 24 h[c]			
Treated[a] ($n = 376$)	Dipper	119	51
	Non-dipper	44	162
		McNemar's test, $P = 0.538$	
Untreated[b] ($n = 235$)	Dipper	122	30
	Non-dipper	22	61
		McNemar's test, $P = 0.332$	
(ii) Between the first 24 h and the mean of 48 h[f]			
Treated[d] ($n = 376$)	Dipper	149	21
	Non-dipper	19	187
		McNemar's test, $P = 0.875$	
Untreated[e] ($n = 235$)	Dipper	138	14
	Non-dipper	12	71
		McNemar's test, $P = 0.845$	

[a] 25% of treated patients (95 subjects = 51 + 44) changed their circadian pattern between first and second 24-h monitoring. [b] 22% of untreated patients (52 subjects = 30 + 22) changed their circadian pattern between first and second 24-h monitoring. [c] Comparison of the % of changes between treated and untreated patients: $P = 0.377$. [d] 11% of treated patients (40 subjects = 21 + 19) changed their circadian pattern between the first 24-h monitoring and the whole 48-h period. [e] 11% of untreated patients (26 subjects = 14 + 12) changed their circadian pattern between the first 24-h monitoring and the whole 48-h period. [f] Comparison of the % of changes between treated and untreated patients: $P = 0.869$.

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Table 4 Night-to-day ratio according to the reproducibility of the circadian blood pressure pattern

	Night-to-day ratio			
All patients ($n=611$)	D-D ($n=241$)	D-ND ($n=81$)	ND-D ($n=66$)	ND-ND ($n=223$)
SBP 48 h	0.84 ± 0.04	$0.90 \pm 0.03^{*}$	$0.90 \pm 0.02^{*}$	0.98 ± 0.06
DBP 48 h	0.79 ± 0.05	$0.85 \pm 0.03^{*}$	$0.86 \pm 0.03^{*}$	0.93 ± 0.07
SBP 1st 24 h	0.83 ± 0.04	$0.86 \pm 0.03^{**}$	$0.94 \pm 0.03^{*}$	0.98 ± 0.06
SBP 2nd 24 h	0.84 ± 0.05	$0.94 \pm 0.05^{*}$	$0.87 \pm 0.03^{*}$	0.98 ± 0.07
DBP 1st 24 h	0.79 ± 0.06	$0.81 \pm 0.04^{\#}$	$0.90 \pm 0.05^{\#\#}$	0.93 ± 0.07
DBP 2nd 24 h	0.79 ± 0.06	$0.89 \pm 0.05^{*}$	$0.82 \pm 0.04^{*}$	0.94 ± 0.07

D, dipper; ND, non-dipper. ANOVA among the four groups of patients for all the night-to-day ratios considered: $P<0.0005$. Post-hoc comparisons: $^{*}P<0.0005$, in the post-hoc comparison both with D-D and with ND-ND groups. $^{**}P=0.002$ in the post-hoc comparison with D-D and $P<0.0005$ in the comparison with ND-ND. $^{\#}P=0.001$ in the post-hoc comparison with D-D and $P<0.0005$ in the comparison with ND-ND. $^{\#\#}P<0.0005$ in the post-hoc comparison with D-D and $P=0.002$ in the comparison with ND-ND.

D-D, D-ND, ND-D, ND-ND. Thus, individuals whose circadian profile changed had night/day ratios located between those who were D or ND in both 24-h monitoring periods. A similar pattern was observed when untreated subjects were analysed (data not shown). When graphically analysing the variability of SBP night/day ratios between the first and second 24-h monitoring periods, no systematic variation in the differences between periods was observed over the range of the ratio values, neither globally nor separately for treated and untreated patients (Fig. 3); a similar plot was obtained for DBP ratios.

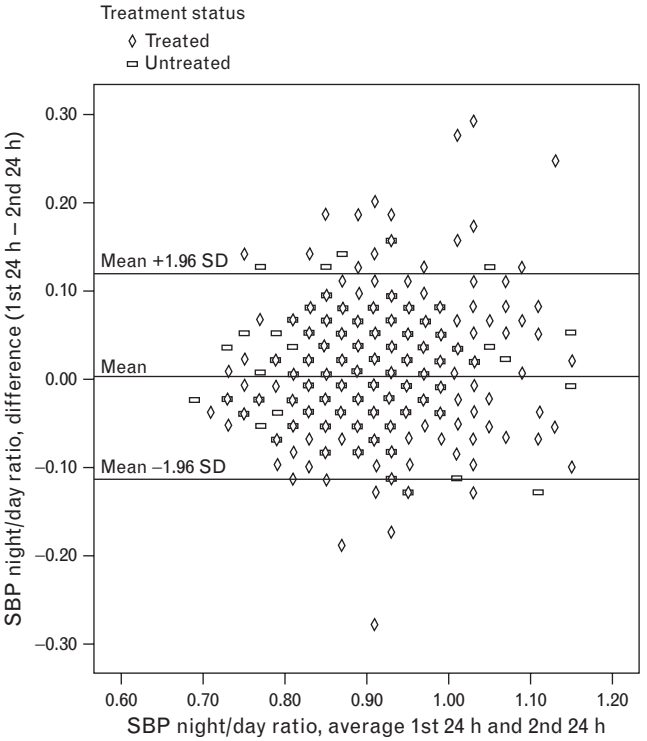
Discussion

The present clinical study compared the reproducibility of the circadian BP profile between two consecutive 24-h ABPM periods and with the mean for 48 h and found that the circadian profile changed in 24% of individuals between the two 24-h periods. This percentage was reduced to 11% when the first 24-h period was compared with a longer monitoring period, the mean of 48 h. These changes in circadian BP profile occurred independently of whether patients were receiving antihypertensive treatment or whether the circadian profile was classified as D or ND (Figs 2 and 3, Table 3).

The degree of reproducibility of the D or ND profile was independent of treatment, confirming the results of the SAMPLE study involving repeated monitoring periods over 1 year in hypertensive patients before and after treatment with lisinopril [17]. Mochizuki *et al.* [18] also reported limited reproducibility of the circadian BP profile recorded over a 48-h period: in 253 untreated hypertensive patients with no cardiovascular complications, the profile changed in 29% of them between the first and second day. Some studies have found that the circadian BP profile is more reproducible in groups of patients with a higher prevalence of non-dipping pattern, as is the case of diabetic subjects [27] or patients with kidney failure [28]. Although we observed no differences in reproducibility according to the circadian profile, only 18% of patients were diabetic and only 2% had renal failure.

The proximity of the two monitoring periods removed the possibility of changes observed as a cause of environmental conditions, such as changes in temperature, body weight or treatment, factors that were not controlled in other studies and can influence BP changes. Unlike our study, where short-term reproducibility is analysed in consecutive 24-h periods, most studies assessing the reproducibility of ABPM compared monitoring periods separated by weeks or months, sometimes with intervening treatment, although the changes observed in the circadian BP profile are similar to our results [7,17,19,21].

Fig. 3



Systolic blood pressure (SBP) night/day ratio: difference versus average of values measured in the first and the second 24-h periods by treatment status. Coefficients of repeatability for SBP night/day ratio: 0.12/0.13/0.10; for all patients/treated patients/untreated patients, respectively. Coefficients of repeatability for diastolic blood pressure (DBP) night/day ratio: 0.14/0.15/0.13 for all patients/treated patients/untreated patients, respectively.

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The differences in mean SBP between the monitoring periods varied between 1 and 2 mmHg for the active period, with lower values at night and for DBP in both periods. These differences during the daytime fall in the middle of the range reported by other authors [20,29] and, in our opinion, are clinically irrelevant for a given subject. Consequently, the use of repeated ABPM or ABPM for periods longer than 24 h should probably be limited in the clinical practice setting to those situations where decisions are made based on BP circadian profile. Some reports [20,29] have suggested that differences in BP between consecutive days could be due to increased BP during the first few hours of monitoring ('the ABPM effect') on the first time that BP is monitored [30].

Although BP is a continuous variable, the reproducibility of the circadian BP profile has mainly been assessed qualitatively as D/ND. Prospective studies where BP has been analysed as a continuous variable have shown a continuous inverse relationship between increased cardiovascular morbidity and mortality and a lower nocturnal decline in BP [14,15]. It is probable that if BP were assessed quantitatively as the night/day ratio, the reproducibility would improve and this might allow better identification of individuals with low reproducibility of the circadian BP profile. Given the limitations of classifying patients as D or ND, we decided to analyse the circadian BP profile as a continuous variable in terms of the night/day ratio, in an attempt to better identify the group of subjects with poor reproducibility. We found that the night/day BP ratio of subjects whose circadian profile changed was significantly different to the ratio of those with a stable profile, both for SBP and DBP (Table 4). Subjects with low reproducibility of ABPM recordings had a night/day BP ratio in both 24-h periods that lay between patients who remained either D or ND. Furthermore, the ratio in individuals with poor reproducibility was closer to the cut-off of 0.9 that defines the circadian BP profile. The variability around the cut-off of the night/day SBP ratio (not the DBP ratio) is mainly responsible for the change in the circadian profile between the first and the second 24-h period.

Assessment of the circadian BP profile in terms of the night/day BP ratio (especially for SBP) can help to identify individuals whose profile is more reproducible. Antihypertensive treatment does not affect the reproducibility of the circadian BP profile analysed according to the night/day ratio (Fig. 3). BP variability, one of the factors that may explain the poor reproducibility of ABPM, is partly dependent upon physical activity, a variable that may differ according to the day of measurement; however, studies of simultaneous activity monitoring do not appear to have found that changes in physical activity explain the changes observed in the circadian BP profile between monitoring periods [31,32]. Sleep quality is another factor that could influence the classification as D or ND, but not all authors agree that this variable influences changes in the circadian BP profile [32]. Finally, the phenomenon of regression to the mean with repeated BP should be taken into account [33].

Many of the factors involved in changes in the circadian BP profile remain to be elucidated and the mechanisms associated with a lack of reduction in the nocturnal BP have not been fully identified; however, it is known that the vascular system of these patients is exposed to a greater haemodynamic load over a 24-h period, leading to increased cardiovascular morbidity and mortality.

The limitations of the study include the clinical setting, which means there were various reasons for performing ABPM. In addition, the physical activity of the subjects and the duration of the daytime and night-time periods were only assessed using the patient diary; however, some studies have shown a good correlation between the hours of rest indicated in the patient's diary and those obtained from actigraph recordings [34], while others have found that differences in BP between consecutive monitoring periods are not accompanied by changes in heart rate or physical activity measured by actigraph [30,31]. Sleep quality was also not measured since patient assessment of this variable is highly subjective; however, patients who did not sleep for a minimum period (from 01.00 h to 05.00 h) or who worked during the night were excluded. Possible variations in the timing of medication were also not assessed, although in all the analyses, no differences were observed in circadian profile variability in the different periods between treated and untreated subjects. Although daytime activity and the duration and quality of sleep are the main determinants of the size of the nocturnal BP reduction, other factors can affect the variability of the circadian BP profile [35]. Finally, when analysing our results, it should be remembered that comparing the results from the first 24-h period and the mean of 48 h means comparing a part with the whole, and that the similarity is, consequently, always greater than when comparing the first and second 24-h periods.

In conclusion, classification as D or ND on the basis of a single 24-h ABPM period is moderately reproducible, given that one in five patients change their profile in the following 24-h period and one in 10 when compared to the mean of the 48-h period. Our results, derived from the analysis of two consecutive 24-h ABPM sessions, suggest that a more reliable classification of the BP circadian profile, at least when used for clinical decision making (non-dippers), should be performed by repeating a second ABPM within a short period.

Despite the proportion of incorrectly classified patients being reduced with 48-h ABPM, its use in clinical practice should be further assessed in terms of cost-effectiveness. Given that the reproducibility of ABPM is worse in

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patients with a night/day BP ratio closer to the cut-off that defines the D/ND profile, identification of the factors involved in the reproducibility of the circadian BP profile is essential in order to more accurately classify individuals as D/ND. Further studies using chronotherapeutic approaches to antihypertensive treatment to determine whether normalization of the circadian BP profile improves cardiovascular prognosis in ND individuals are necessary.

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There are no conflicts of interest.

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